25 April 2013
EMA/370014/2013
Committee for Medicinal Products for Human Use (CHMP)

Capecitabine SUN

(capecitabine)

Procedure No. EMEA/H/C/002050/0000

Sun Pharmaceutical Industries Europe B.V.

Assessment report for initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

AEs	adverse events
Alu/Alu	Aluminium /Aluminium
ANOVA	analysis of variation
AP	Applicant's Part (or Open Part) of a DMF/ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC_{0-t}	area under the curve from time 0 to time t
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
BP	British Pharmacopoeia
BSE	bovine spongiform encephalopathy
C_{max}	maximum concentration
CEP	Certificate of Suitability of the Ph.Eur.
EP or Ph. Eur.	European Pharmacopoeia
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
GC	gas chromatography
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
IPC	In-process control test
IR	Infrared
LLOQ	lower level of quantification
LOA	Letter of Access
LOD	Limit of Detection

LOQ	Limit of Quantification / Quantitation
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PIL	Patient Information Leaflet
PK	pharmacokinetics
QOS	Quality Overall Summary
RH	Relative Humidity
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
SAEs	serious adverse events
t½	half life
t_{max}	time to maximum (plasma) concentration
TGA	Thermo-Gravimetric Analysis
ThyPase	thymidine phosphorylase
TSE	transmissible spongiform encephalopathy
UV	Ultraviolet
XRD	X-Ray Diffraction
USP	US Pharmacopeial Convention
5-FU	5-fluorouracil

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 31 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Capecitabine SUN, through the centralised procedure under Article 3 (3) of Regulation (EC) No 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2009.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

"Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.

Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated."

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xeloda instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Xeloda 150 and 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 02/02/2001
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/00/163/001-002

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xeloda 150 and 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 02/02/2001
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/00/163/001-002

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xeloda 500 mg film-coated tablets
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 02/02/2001
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/00/163/002

- Bioavailability study number(s): PKD_11_322

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Sun Pharmaceutical Industries B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: John Joseph Borg

- The application was received by the EMA on 31 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012.
- During the meeting 15-18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 October 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2013.
- During the CHMP meeting on 18-21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 27 March 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 April 2013 and updated 22 April 2013.
- During the meeting on 22 – 25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Capecitabine SUN.

2. Scientific discussion

2.1. Introduction

Capecitabine SUN, 150 mg and 500 mg film-coated tablets is a generic application made according to Article 10(1) of Directive 2001/83/EC.

The active substance in Capecitabine SUN is capecitabine, a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

The efficacy and safety of capecitabine has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference medicinal product Xeloda.

The indication proposed for Capecitabine SUN is the same as the authorised indication for the reference medicinal product and includes treatment of colon, colorectal, gastric and breast cancer.

Given as single agent, the recommended starting dose for capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

In combination treatment in colon, colorectal and gastric cancer, the recommended starting dose of capecitabine should be reduced to 800 – 1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m^2 twice daily when administered continuously. The inclusion of biological agents in a combination regimen has no effect on the starting dose of capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the capecitabine plus cisplatin combination. Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of 6 months.

Finally, in combination with docetaxel, the recommended starting dose of capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. For further posology recommendations please refer to section 4.2 of the SmPC.

The proposed pack sizes are consistent with the dosage regimen and duration of use of the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as film-coated tablets containing 150 mg and 500 mg of capecitabine as active substance.

Other ingredients as defined in the SPC section 6.1 are for the tablet core: talc, anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate and for the tablet coating: hypromellose, titanium dioxide, lactose monohydrate, macrogol, yellow iron oxide and red iron oxide.

The tablets are packed in Alu /Alu blisters in packs of 60 tablets for the 150 mg strength and 120 tablets for the 500 mg strength.

2.2.2. Active substance

The active substance of Capecitabine SUN is capecitabine, which has the chemical name: pentyl N-{1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-methyloxolan-2-yl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl}carbamate. It corresponds to the molecular formula $C_{15}H_{22}FN_3O_6$ and relative molecular mass of 359.35. It appears as white to off-white non hygroscopic crystalline powder which is sparingly soluble in water and freely soluble in methanol. Its pKa has been determined as 8.77.

Capecitabine has chiral properties and the molecule contains four stereogenic centers. The configuration matches with the corresponding positions 5-deoxy-β-D-ribofuranosyl. And has a specific rotation between +96.0° and +100.0° for a 1.0 % w/v solution in methanol (20º C, Sodium D line).

A physical characterization report regarding the crystal structure of capecitabine has been presented. It has been shown that, capecitabine manufactured by the active substance supplier is consistent with regard to the crystalline form. No other polymorphic forms are stated to be known in the literature.

Manufacture

An ASMF has been submitted for the drug substance.
The manufacture of capecitabine is comprised of three main steps including a purification step. The synthetic process is sufficiently described in the ASMF, the choice of the starting materials

has been justified and so have been the process controls, specifications and test methods. There are two proposed batch sizes.
Satisfactory information on the validation production batches, on the manufacturing process development and on the methods used in the control of the starting materials were also provided. The ASMF holder has adequately discussed the potential carry-over of all reagents, solvents and impurities and their presence in the final drug substance.
Detailed information regarding the control of starting materials, reagents and raw materials as well as the control of critical steps and intermediates is provided in the ASMF.

Specification

The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), identification (IR, HPLC), solubility and pH (Ph.Eur.), colour index (UV), assay (HPLC), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur.), related substances (HPLC), residual solvents (GC), specific optical rotation (Ph.Eur.), water (Ph.Eur.) and particle size distribution (laser light diffraction). The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data is presented in the ASMF for three batches for each proposed batch size. All the results reported are all within proposed specifications.

Stability

Three production scale batches of capecitabine have been placed on accelerated (40±2°C/75±5% RH) and long term (25±2°C/60±5% RH) conditions according to ICH guidance.

The batches are packaged in double low density polyethylene bag under nitrogen atmosphere. Appearance, identification, water content, specific optical rotation, related substances, assay, colour index and pH were monitored during the stability studies. The related substances method has been shown to be stability indicating.

Up to 18 months of long term and six months of accelerated data were reported. No significant changes in any of the parameters studied were observed and all results were within the proposed specifications under either the long term or the intermediate conditions.

Also after six months at the accelerated condition, all results for the parameters studied were within the proposed specifications.

Photostability and forced degradation studies for the drug substance demonstrated that the drug substance can be considered photo-stable in the solid state.

Stress studies were also performed. Capecitabine was found stable under thermal and UV exposure at 254 nm and 366 nm stress condition but is found to degrade, when exposed to acid, alkali and peroxide.

Based on the overall stability data the proposed re-test period and storage conditions are supported.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the product development was to formulate a medicinal product robust, stable and bioequivalent to the reference medicinal product. Several formulations trials were conducted to improve in vitro drug dissolution and other physicochemical properties of drug product during development. All excipients included in the formula are commonly used in the pharmaceutical industry and most of them are qualitatively the same as for the reference product Xeloda. No novel excipients are used.

A number of formulation changes were proposed during the optimisation studies by varying the amounts of mainly disintegrant and binder and two pilot bioequivalence studies were performed as part of the optimisation studies. The design of these pilot bioequivalence studies was appropriate. Based on the results of these pilot studies the amounts of the above excipients were established. Subsequently the formulation was slightly modified with incorporation of intragranular phase.

The dissolution method used for routine testing has been shown to be reasonably discriminatory versus manufacturing process changes and is considered acceptable as a routine dissolution test method.

In-vivo bioequivalence has been shown between 500mg strength of test and reference and is considered acceptable. The dissolution profiles of the Capecitabine SUN 500 mg film coated tablets and of the reference Xeloda 500 mg used in the bioequivalence study have been compared in order to demonstrate similarity.

A biowaiver has been applied for the lower strength 150 mg. The dissolution profiles of Capecitabine SUN 150 mg tablets were compared with the 500 mg test biobatch as required by the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Dissolution profile similarity between the 150mg and 500mg test products has been evaluated by the model independent (multivariate confidence region procedure) and model dependent (Weibull model) methods using dissolution profile comparison software DDsolver. The methods where very well explained, and results clearly presented and validation data have also been presented. Both methods demonstrated the dissolution profile similarity between the 150mg and 500mg strength and since all other criteria as per the Bioequivalence Guideline are met, the biowaiver for the 150mg strength can therefore be accepted.

For the development of the manufacturing process the fact that capecitabine is an antineoplastic drug substance was considered in order to minimize the exposure of the active to human as well as exposure to environment during handling.

The manufacturing process includes a wet granulation step which is considered a critical step. The operating ranges for granulations step parameters have been established based on a two level four factor full factorial design of experiments in lab scale batches.

Adventitious agents

Apart from lactose, no TSE risk materials are used in the manufacture of the finished product. It has been confirmed by the manufacturer of the lactose that it is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev2. Appropriate TSE/BSE free declarations were provided.

Manufacture of the product

The finished product is manufactured by a standard process comprising wet granulation, drying, blending, tablet compression and film-coating using standard equipment. The manufacturing process has been validated and data for production scale batches presented. Granulation has been identified as a critical step. Suitable in-process controls are put in place to guarantee reproducible product quality.

Process validation has been performed on three commercial scale batches for each strength of capecitabine film-coated tablets. The results of the process validation are sufficient to support the robustness of the manufacturing method. Batch analysis results of two full scale batches for each strength strength confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Product specification

The finished product release and shelf-life specifications includes tests and limits for appearance (visually), identification of drug substance (HPLC, IR), identification of colorants (titanium dioxide, iron oxide: chemical reaction) disintegration (Ph.Eur.), average weight (Ph.Eur.), uniformity of dosage units (Ph.Eur.), water content (Ph.Eur.), dissolution (Ph.Eur.), and microbial purity (Ph.Eur.), related substances (HPLC), assay (HPLC) and microbiological quality (Ph.Eur).

The limits for two specified impurities are above the qualification limits of the ICH Q3B guideline. However, since those two impurities are human metabolites, the limits for these impurities are considered acceptable and are considered to have been toxicologically qualified.
Batch analysis data have been presented for two commercial scale batches of finished product of both strengths. All results reported were within proposed specifications confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Primary stability studies according to ICH guidance have been initiated on two production scale batches of each strength. The batches are packaged in the proposed blister package and have been stored under long term (25±2 ^{0}C/ 60±5% RH) and accelerated (40±2 ^{0}C/ 75±5 %RH)

conditions. Stability data in long term conditions have been presented for up to 12 months and for six months under accelerated conditions. The same methods are used as for the release testing and the following parameters have been tested: appearance, identification, dissolution, uniformity of dosage units, assay, related substances, water content, disintegration and microbial limits.
Both in the long term and accelerated conditions capecitabine tablets comply with all specifications for the parameters monitored in the study.
A photostability study according to ICH guidance has been performed on one batch of the 500 mg strength. Results were found to meet the specifications.

Based on the overall results the proposed shelf-life and storage conditions have been are supported.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Capecitabine SUN manufactured by Sun Pharmaceutical Industries Europe B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all capecitabine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

Capecitabine SUN has been formulated utilising conventional pharmacopoeial excipients the safety profile of which has been established. Product impurity profiles have been discussed and the percentage impurity content is considered acceptable.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to the approval of Capecitabine SUN from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing capecitabine. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fed conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) in their current version, are of particular relevance.

GCP

The applicant has provided a statement to the effect that the clinical trial (bioequivalence study) conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence study was carried out on the Capecitabine 500mg film coated tablets. Based on this study, the applicant has requested a biowaiver for 150mg tablets and has provided

justification based on the five criteria as mentioned in the Guideline on the Investigation Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1).

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

2.4.2. Pharmacokinetics

Study CPB 500T IR 3265 11(a): a randomised, open label, two treatment, four period, two sequence, replicated crossover, single dose comparative oral bioavailability study to establish comparative bioequivalence of Capecitabine 500mg film coated tablets manufactured by SUN Pharmaceutical Industries Limited and Xeloda 500mg tablets manufactured by Roche Registration Limited UK in cancer patients under fed conditions.

Methods

Study design

This study was conducted in five different clinical sites in India. Two treatments and two sequences were used in the four period study performed over four days. Subjects were administered either Test or Reference product of Capecitabine 500 mg tablet (multiples according to dosage as shown below), with 240 mL (±2mL) of water at room temperature, 30 minutes after administration of high fat high calorie breakfast (as recommended in the EMA bioequivalence guideline) in the morning on day 1 (period I), day 2 (period II), day 3 (period III) and day 4 (period IV) according to the randomisation schedule. All subjects who were dosed with the study drug had received Inj. Granisetron 2 mg IV, 30 minutes (±10 minutes) before dose administration of capecitabine.

Test and reference products

Patients received the following dose (1250mg/m^2 as multiples of 500mg tablets) of the test or the reference product of capecitabine 500mg tablets as per their body surface area as shown below:

Dose Level 1250 mg/m^2 Twice a Day		Number of Tablets to be given at 500 mg Dose (Each Morning and Evening)
Surface Area (m2)	Total Daily* Dose (mg)	
≤1.26	3000	3
1.53 – 1.66	4000	4
1.93 – 2.06	5000	5

*Total Daily Dose divided by 2 to allow equal morning and evening doses.

The four periods were separated by a wash-out phase of about 12 hours. In evening dose, the patients received their usual dose of Capecitabine tablet as per their dosing regimen.

Capecitabine 500mg film tablets, manufactured by Sun Pharmaceuticals Industries India has been compared to Xeloda 500mg Tablets, manufactured by Roche Registration Ltd UK.

Certificates of analysis for both the test and reference products have been appended.

Population studied

50 male and female human subjects were enrolled as per the protocol. The study started with 50 and 47 subjects completed the study.

The subjects ranged in age from 32 to 71 years, with a mean age of 48.7 years. Mean body weight of these subjects was 55.27 kg with a range of 35.0 to 90.0 kg. Mean Height of these subjects was 154.87 cm with a range of 141.3 to 169.0 cm. Mean BSA of these subjects was 1.534 m^2 with a range of 1.18 to 2.03 m^2. All subjects fulfilled the inclusion and exclusion criteria.

Analytical methods

Analysis of plasma concentrations of capecitabine were measured by a validated analytical method using High Performance Liquid Chromatography coupled with tandem Mass Spectrometry.

The subject sample analysis was performed between 24 January 2012 and 25 April 2012, including re-assays. 3085 study samples were analysed and the number of samples analysed including repeat analysis through 52 accepted runs were 4325 (3805+520). 52 accepted runs had 520 Quality Control samples. The total numbers of Quality Control samples analysed was 13.7% of the total number of study samples analysed.

The analytical method has been validated and the following parameters were addressed; selectivity of capecitabine and fexofenadine (IS), interference from granisetron, calibration curve (linearity), recovery, precision, accuracy, dilution integrity, stability of the stock solution (short and long term, bench top, freeze-thaw, dry extract, in-injector stability), ruggedness, specificity and matrix effect. Standard Assay range for capecitabine (6 replicates used): 49.9ng/mL to 9986.8ng/mL whilst the Standard Assay range for capecitabine used in the actual method, (6 replicates used): 50.1ng/mL to 9970.0ng/mL.

A total of 4057 samples were collected in the four periods and 3805 presented valid results. 111 were re-assayed and 300 were used for incurred sample reanalysis. 95.0% of the samples scored less than 20% difference between the two values.

Pharmacokinetic variables

The pharmacokinetic parameters of this trial were:

- Parametric ANOVA on Cmax, Tmax, AUC0-t, AUC0-∞, Kel and T½, Geometric confidence intervals for Cmax, AUC0-t, AUC0-∞;
- Non-Parametric Wilcoxon signed rank test performed on un-transformed Tmax data;

- Terms in the ANOVA model: dose, group, sequence, subject (dose*group*sequence), period (dose*group), treatment, (group*treatment) interaction;
- ln transformed parameters: Cmax, AUC0-t, AUC0-∞.

Statistical methods

Pharmacokinetic data of 44 subjects who completed the study were included for statistical analysis. The analyses included summary statistics, ratio analysis, analysis of variance (ANOVA), intra-subject variability, 90% confidence intervals and power analysis for capecitabine.

Due to the use of multiple sites and groups, it was not expected that within groups there will not be patients receiving a particular sequence. This was not planned for in the protocol and the study was imbalanced as all the five groups for each of three doses did not contain at least one subject for both the sequences (i.e. ABAB, BABA) due to which the statistical model parameters could not be estimated. The problematic groups were dose 1500 mg (group 3), dose 2000 mg (group 6) and dose 2500 mg (group 1, 3, 4, 6) as shown in the table below.

Table 1: Statistical model parameters

Subject Number										
Dose	Group									
	1		2		3		4		6	
	Sequence		Sequence		Sequence		Sequence		Sequence	
	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA
1500	13	5	21	23	49	⊗	33	47	29	27
		11			50					30
Dose	Group									
	1		2		3		4		6	
	Sequence		Sequence		Sequence		Sequence		Sequence	
	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA
2000	4	6	19	16	39	36	31	34	28	⊗
	7	9	20	17	40	37	35			
	8	14		18	42	38	46			
	10			24	44	41				
	12					43				
	15									
Dose	Group									
	1		2		3		4		6	
	Sequence		Sequence		Sequence		Sequence		Sequence	
	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA	ABAB	BABA
2500	⊗	⊗	22	25	⊗	48	⊗	⊗	⊗	⊗

⊗ group which don't contain at least one subject for both the sequences.

Thus to achieve a balance and to estimate least sequence means for treatment and ANOVA precisely, pseudo- groups were then formed by combining the data of subjects receiving 2500 mg to the respective groups of subject receiving 2000 mg. Also, the data of subject number 30 was combined with group 3 and subject number 36 was combined with group 6 for the same. Subject number 30 and 36 were chosen for combining their data as their dosing dates (12/01/12 and 20/12/11) of these subjects were closest to dosing date of subjects in the

respective chosen groups. The sequence of treatment administration of these subjects was kept unchanged while pseudo grouping.

Results

Table 2: Pharmacokinetic parameters for Capecitabine (non-transformed values)

Pharmacokinetic parameter	Test			Reference		
	geometric mean	SD	CV %	geometric mean	SD	CV %
$AUC_{(0-t)}$	7528.0936	2029.66128	27.0	7740.0708	2365.35601	30.6
$AUC_{(0-\infty)}$	7678.4267	1993.18713	26.0	7992.5408	2643.73144	33.1
C_{max}	7201.68	3668.887	50.9	8238.28	5818.240	70.6
T_{max}*	1.333			1.417		
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours					
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity					
C_{max}	maximum plasma concentration					
T_{max}	time for maximum concentration (* median, range)					

Table 3: Statistical analysis for Capecitabine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	98.25	94.60 to 102.05	14.66
$AUC_{(0-\infty)}$	97.17	92.97 to 101.56	16.89
C_{max}	95.10	85.73 to 105.49	41.52
* estimated from the Residual Mean Squares			

Safety data

There were no pre-treatment adverse events observed in this study. There were no adverse events observed in period I and III. Out of the 50 subjects, 4 subjects (8.0%) experienced 5 post-dose adverse events in this study. Of these 5 adverse events, 2 adverse events were single treatment emergent in period II and the 3 remaining adverse events (which occurred in period IV) were considered to have emerged from both formulations.

Conclusions

The 90% confidence intervals calculated for the primary parameters Cmax, AUC0-∞ and AUC0-t for capecitabine fall within the 80.00 – 125.00% acceptance range after appropriate dose administration under fed conditions (in line with the originator SmPC). Based on the presented bioequivalence study Capecitabine SUN is considered bioequivalent with Xeloda.

The results of study CPB 500T IR 3265 11(a) with the 500mg formulation can be extrapolated to the other strength, 150 mg, according to conditions in the Guidelines.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

As mentioned earlier, two pilot bioequivalence studies were performed as part of the formulation optimisation studies. These studies were not submitted, but they were discussed by the applicant upon CHMP request. The design of the first pilot study (two-way cross over) was considered appropriate for the intended purpose and the results (showing lower bioavailability of test formulation compared to reference product, data not shown) allowed improvement of both formulation (as discussed in the Pharmaceutical development section) and study design of the bioequivalence study. The changes to the bioequivalence study design were tested in the second pilot study which included a higher number of sampling time-points in the initial phase for better characterisation of Cmax and AUC (due to rapid drug absorption and faster rate of elimination) and a replicate design to overcome the high intra-subject %CV for reference product. The second pilot study concluded that the tested design (reference replicated or fully replicated with more closure time points at initial phase) can characterise PK parameters adequately so that the pivotal BE study (using this design) can be conclusive.

In the pivotal study, the absence of two subjects' samples for period II and one for period IV (total three subjects) were not considered to have any significant impact on the study by the applicant; however, concentration data and pharmacokinetic parameters from such subjects were requested in the individual listings in line with the Guideline on the investigation of Bioequivalence section 4.1.8.

A total of 4057 samples were collected in the four periods and 3805 presented valid results. 111 were re-assayed and 300 were used for incurred sample reanalysis. 95.0% of the samples scored less than 20% difference between the two values. This was considered acceptable.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study results, Capecitabine 500mg tablets, manufactured by SUN Pharmaceuticals and Xeloda 500mg tablets, of Roche Registration Ltd, are considered bioequivalent in cancer patients under fed conditions. The results of the bioequivalence study with the 500mg formulation can be extrapolated to the other strength, 150 mg, according to conditions in the Guidelines.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

A risk management plan has not been submitted with the application. This is acceptable as there are no current safety issues with use of capecitabine tablets which would require additional risk minimization activities. Routine pharmacovigilance is considered sufficient for safety monitoring.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of capecitabine film coated tablets. The reference product Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, the treatment of metastatic colorectal cancer, the first-line treatment of advanced gastric cancer in combination with a platinum-based regimen; in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy (previous therapy should have included an anthracycline) and as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. No nonclinical studies have been provided for this application but an adequate summary of the

available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomised, two treatment, four period, two sequence, replicated crossover, single dose comparative design in the fed state. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Capecitabine SUN met the protocol-defined criteria for bioequivalence when compared with theXeloda. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Capecitabine SUN in the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, the treatment of metastatic colorectal cancer, the first-line treatment of advanced gastric cancer in combination with a platinum-based regimen; in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy (previous therapy should have included an anthracycline) and as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

Not applicable.